## REMARKS

Applicant respectfully requests reconsideration and allowance of all pending claims.

### I. Status of the Claims

Claims 1-23 remain pending in this application.

### II. 35 U.S.C. 103(a) Rejection

Reconsideration is requested of the rejection of claims 1-23 under 35 U.S.C. §103 as being obvious in view of the combination of Midha et al. (U.S. Patent No. 6,127,385) and Epstein et al. (U.S. Patent Publication No. 2002/0103162).

#### A. The Claimed Subject Matter

The present application is directed to a methylphenidate solution (e.g., a solution of the free base or a pharmaceutically acceptable salt thereof) that has improved chemical stability, and therefore improved shelf-life or **storage stability** as well. (See, e.g., paragraphs [0001] and [0010].) As noted in the present application, Applicant has discovered that by preparing a solution of methylphenidate using a solvent system comprising a combination of water and a non-aqueous solvent, and in particular a **solvent system** comprising **less than about 50% water** (or alternatively **greater than about 50% of the non-aqueous solvent**), the chemical stability, and therefore the shelf-life or storage stability, of the solution is improved. (See, e.g., paragraphs [0008] and [00010].) As illustrated in Applicant's working examples, such solutions have been observed to have an improved shelf-life or storage stability, including a projected shelf-life of at least two years. (See, e.g., paragraph [00021] and Examples 1-3.)

More particularly, the claims of the present application are directed to the following:

> Claim 1, from which claims 2-8 depend, is directed to a methylphenidate solution comprising, in relevant part, methylphenidate and at least one pharmaceutically acceptable organic acid dissolved in a **solvent system**, the solvent system **comprising between about 10% and about 45% water** and **at least about 50%** of at least one **non-aqueous solvent**.
>
> Claim 9, from which claims 10-13 depend, is directed to a methylphenidate HCl solution comprising, in relevant part, methylphenidate HCl and at least one organic acid dissolved in a **solvent system**, the solvent system comprising **less than about 50% water**, between **about 30% and about 70%** of at least one **polyol** solvent, and between **about 10% and about 70%** of at least one **glycol** solvent.

Claim 14, from which claims 15-18 depend, is directed to a methylphenidate HCl solution comprising, in relevant part, methylphenidate HCl and at least one organic acid dissolved in a **solvent system**, the solvent system comprising between **about 10% and about 45% water**, between **about 40% and about 60%** of at least one **polyol** solvent, and between **about 10% and about 30%** of at least one **glycol** solvent.

Claim 19, from which claims 20-23 depend, is directed to a methylphenidate HCl solution comprising, in relevant part, methylphenidate HCl and at least one organic acid dissolved in a **solvent system**, the solvent system comprising between **about 30% and about 40% water**, between **about 45% and about 55%** of at least one **polyol** solvent, and between **about 10% and about 20%** of at least one **glycol** solvent.

**B. The Cited Art**

Midha et al. disclose a method of treating depression in a patient by oral or non-oral administration of the active 1-threo-methylphenidate, which may be in the form of the free base or a pharmaceutically acceptable salt. (See, e.g., column 1, lines 5-8, and column 2, lines 36-38). Although they make a general reference to a solution containing the active, ascorbic acid, and an aqueous or non-aqueous solvent (see, e.g., column 4, lines 59-63), they **fail to disclose or suggest** a solution comprising the active in a **solvent system** that in turn comprises both water and a non-aqueous solvent, **wherein the concentration of water therein is less than about 50%**.

Furthermore, it is to be noted that Midha et al. **do not make any specific reference at all** to the concentration of water, or the concentration of the non-aqueous solvent, in a solution that contains both in combination with the active. Applicant respectfully submits this is because Midha et al. are simply not concerned with the storage stability or shelf-life of such a solution. Evidence of this may be found in the fact that they **do not even reference storage stability** or shelf-life as factors to be considered when preparing such a solution. Rather, they are interest in the **administration** of their solutions or compositions.

Epstein et al. disclose methods and compositions for enhancing long-term memory function and/or performance. (See, e.g., paragraph [0006].) Although they make a general reference to the preparation of a solution of a methylphenidate compound using, among other things, water, a polyol or a mixture thereof (see, e.g., paragraph [0250]) as a solvent, like Midha et al., they also fail to disclose or suggest a solution comprising the active in a **solvent system** that in turn comprises both water and a non-aqueous solvent, **wherein the concentration of water therein is less than about 50%**.

Furthermore, it is to be noted that Epstein et al. **do not make any specific reference at all** to the concentration of water, or the concentration of the non-aqueous solvent, in a solution that contains both in

combination with the active. Applicant respectfully submits this is because Epstein et al., like Midha et al, are simply not concerned about the storage stability or shelf-life of such a solution. Evidence of this may be found in the fact that **they do not even reference storage stability** or shelf-life as factors to be considered when preparing such a solution. Rather, they too are interest in the **administration** of their solutions or compositions.

These interpretations of the Midha et al. and Epstein et al. references are further supported by the declaration of Clifford J. Herman, submitted with this response. Mr. Herman is the sole inventor of the present application. In his declaration, Mr. Herman states that a completely aqueous solvent system (or even a solvent system that includes greater than about 50% water) is not suitable for a methylphenidate solution, due to problems with solubility and storage stability. Mr. Herman also states he discovered that, in order to preserve the storage stability of the methylphenidate solution, the solution needs to comprise less than about 50% water (or alternatively, greater than about 50% of a non-aqueous solvent). Furthermore, Mr. Herman states that both of the cited references fail to recognize or acknowledge that methylphenidate solutions are inherently unstable, and that none of the solutions or compositions disclosed in the working Examples or described anywhere else therein comprise less than about 50% water (or alternatively, greater than about 50% of the non-aqueous solvent). As a result, there is no reason to believe that any of the solutions prepared in the cited references are storage stable.

Additionally, with regard to dependent claim 2 and independent claims 9, 14, and 19, Mr. Herman states that the cited references also fail to recognize the benefit of including the recited concentrations of an organic acid in the methylphenidate solution, in order to further stabilize the solution. Specifically, as noted in the declaration by Mr. Herman, the addition of an organic acid (e.g., citric acid) to the methylphenidate solution at the recited concentration (e.g., a concentration of from about 0.5 mg/ml to about 5.0 mg/ml) enables better control of the pH of the methylphenidate solution, which further stabilizes the solution. While Epstein et al. list citric acid as a metal chelating agent (see, e.g., U.S. Patent Application Publication No. 2002/0103162 at paragraph [0274]), there is no suggestion in the cited reference of using citric acid, or any other organic acid, as a stabilizing agent. Furthermore, there is no suggestion to use an organic acid in the amounts recited in Applicant's claims 2, 9, 14 and 19.

### C. The Claimed Subject Matter is Not Obvious

As set forth in M.P.E.P. §2143, in order for the Office to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art references, when combined, must teach each and every element of the claim; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references; and (3) there must be some reasonable expectation of success. Applicant respectfully submits the Office has failed to establish a *prima facie*

case of obviousness, because (i) each and every element of the claims has not been disclosed or suggested, and/or (ii) motivation is simply not provided to prepare the claimed storage stable methylphenidate solution.

Applicant submits that Midha et al. and Epstein et al., both alone and in combination, fail to disclose or suggest a storage stable solution comprising, among other things, methylphenidate, or methylphenidate HCl, and a solvent system that has a water concentration of less than 50%. More specifically, the combination of Midha et al. and Epstein et al. fail to disclose a storage stable solution comprising such a solvent system, wherein:

(i) the water concentration is between about 10% and about 45% and the non-aqueous solvent concentration is at least about 50% (Claim 1);

(ii) the water concentration is less than about 50%, the polyol concentration is between about 30% and about 70%, and the glycol concentration is between about 10% and about 70% (Claim 9);

(iii) the water concentration is between about 10% and about 45%, the polyol concentration is between about 40% and about 60%, and the glycol concentration is between about 10% and about 30% (Claim 14); or,

(iv) the water concentration is between about 30% and about 40%, the polyol concentration is between about 45% and about 55%, and the glycol concentration is between about 10% and about 20% (Claim 19).

Notably, both Midha et al. and Epstein et al. **fail to disclose or suggest any specific details** relating to a **storage stable** solution comprising methylphenidate as the active in combination with water and another non-aqueous solvent; that is, neither reference provides details of the water content or the non-aqueous solvent content in such a solution.

Applicant also submits that there is simply **no reason or motivation** for one of ordinary skill in the art to modify the disclosures of Midha et al. and Epstein et al. in order to prepare a storage stable solution comprising a solvent system as recited in any one of claims 1, 9, 14 or 19, because **neither Midha et al. nor Epstein et al. provide any link between the solutions they generally reference and storage stability or shelf-life thereof.** In fact, as previously noted above, they do not even identify storage stability or shelf-life as a factor to be considered when preparing such solutions.

Applicant notes the Office's assertion, citing *In re Aller* (105 USPQ 233, 235 (CCPA 1955)), that:

> it is obvious to vary and/or optimize the amounts . . . of aqueous and non-aqueous solvents . . ., **according to the guidance provided** by Midha et al. and Epstein et al. to provide a composition having the desired properties such as the desired concentrations and

> percentages of each component to formulate an effective methylphenidate solution **for administration**. (See the previous Office action at page 4, first full paragraph and, further, present Office action at page 4, last paragraph. Emphasis added.)

However, Applicant respectfully submits that providing guidance for preparation of a solution of methylphenidate for "administration" is not the issue here. Rather, the issue is providing motivation to prepare a solution having improved storage stability and shelf-life, and thus having the composition as claimed. As noted in MPEP §2144.05(II)(B), **a particular parameter must first be recognized as a result-effective variable** before the determination of the optimum or workable ranges of the parameter might be characterized as routine experimentation. (Citing *In re Antonie*, 195 USPQ 6 (CCPA 1977).) Notably, **neither Midha et al. nor Epstein et al. make such a recognition.** More specifically, nowhere in either reference is the storage stability and shelf-life of a methylphenidate solution even mentioned. As such, Applicant respectfully submits Midha et al. and Epstein et al. fail to provide a reason or the guidance, and therefore the motivation, to prepare a solution having the concentrations of aqueous and non-aqueous solvents in the ranges as required in any one of Applicant's claims 1, 9, 14 or 19.

In view of the foregoing, Applicants respectfully submit that the Office has failed to meet its burden in establishing a *prima facie* case of obviousness here, because (i) each and every element of the claimed storage stable solution has not been disclosed or suggested by the combination of Midha et al. and Epstein et al., and/or (ii) motivation is simply not provided by the combination of Midha et al. and Epstein et al. to prepare a storage stable solution as claimed. Therefore, reconsideration of the rejection of claim 1-23 is respectfully requested.

## CONCLUSION

In view of the foregoing, Applicant respectfully requests favorable reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge Deposit Account 13-1160 for any fees due for the submission of this Letter to the Patent Office, as well as the Declaration and/or Request for Continued Examination being filed simultaneously herewith.

Respectfully submitted,

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